Drug Monograph

Generic Name: morphine sulfate extended-release
Trade Name: MorphaBond® ER
Dosage Form: Extended-release tablet
NDCs: 65597-0301-10, 65597-0302-10, 65597-0303-10, 65597-0304-10
Manufacturer: Inspirion Delivery Sciences LLC/Daiichi Sankyo, Inc.
ADF Product Classification: Physical/Chemical Barrier

Executive Summary

MorphaBond® ER (morphine extended-release) is an opioid agonist that is Food and Drug Administration (FDA)-approved for the management of pain that is severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate. This agent, like other long-acting opioids, should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. It is not indicated for use on an as-needed basis.[1] MorphaBond® ER (morphine extended-release) is being evaluated by the Drug Formulary Commission, as it is a relatively new FDA-labeled abuse-deterrent formulation (ADF) in the marketplace to be considered for inclusion on the Massachusetts formulary of interchangeable abuse-deterrent drugs, as outlined in Chapter 258 of the Acts of 2014.

The efficacy and safety of MorphaBond® ER (morphine extended-release) is based upon safety and efficacy data of MS Contin® (morphine extended-release), as MorphaBond® ER (morphine extended-release) was developed under the 505 (b)(2) pathway and demonstrated bioequivalence to MS Contin® (morphine extended-release).[2] MorphaBond® ER (morphine extended-release) is formulated as an extended-release tablet with physicochemical properties that are expected to reduce abuse by the intranasal and oral routes of administration.[1] The abuse-deterrent technology platform used to formulate MorphaBond® ER (morphine extended-release) is referred to by the manufacturer as SentryBond®, and it is designed to maintain the intended release profile of the extended-release opioid contained in the formulation when subjected to physical manipulation or attempts to extract chemically.[3]

In vitro manipulation and extraction study data indicates that attempts to crush or cut MorphaBond® ER (morphine extended-release) tablets is difficult using all but one household tool, and attempts to dissolve the manipulated tablets results in formation of a viscous material that is not able to pass through a syringe. In addition, a relatively low amount of morphine was extracted from intact and ground MorphaBond® ER (morphine extended-release) tablets using a panel of solvents, and appears to release active ingredient slower than other comparable ADFs. Results from an intranasal clinical abuse potential study in 27 nondependent opioid users indicate that crushed MorphaBond® ER (morphine extended-release) was associated with statistically significant lower maximum drug liking scores (E_{max}) compared to crushed MS Contin® (morphine extended-release) (71.13 versus 84.79, respectively; $P<0.0001$). E_{max} for willingness to take drug again was also significantly lower for crushed MorphaBond® ER (morphine extended-release) compared to crushed MS Contin® (morphine extended-release) (66.6 versus 76.5, respectively; $P=0.0341$).[2,4]

Reference Data

MorphaBond® ER (morphine extended-release) is an extended-release tablet formulation of morphine. Morphine is an opioid agonist that is relatively selective for the μ opioid receptor; although, other opioid receptor subtypes may be stimulated at higher doses.[1] Stimulation of the μ opioid receptors results in analgesia, decreased gastrointestinal motility, euphoria, physical dependence, respiratory depression and sedation.[5] The abuse-deterrent properties of MorphaBond® ER (morphine extended-release) are most comparable to those of OxyContin® (oxycodone extended-release) and Hysingla ER® (hydrocodone extended-release) in that all three of these medications are formulated as tablets that resist crushing, cutting or breaking, and attempts to dissolve these formulations results in the formation of a viscous material that resists passage through a needle.[1,6,7] Similar drugs within the long-acting opioid class are listed in Table 1.

Table 1. Long-Acting Opioid Availability[8,9]

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Buprenorphine (Belbuca®, Butrans®)	-	✓
Fentanyl (Duragesic®)	-	✓
Hydrocodone (Hysingla ER®)	✓	✓
Hydrocodone (Vantrela® ER)	✓	✓*
Hydrocodone (Zohydro ER®)	-	✓
Hydromorphone (Exalgo®)	-	✓
Levorphanol (Levo-Dromoran®)	-	✓
Methadone (Diskets Dispersible®, Dolophine®, Methadose®, Methadone Intensol®)	-	✓
Morphine sulfate (Avinza®, Kadian®, MS Contin®)	-	✓
Morphine sulfate (Arymo® ER)	✓	✓*
Morphine sulfate (MorphaBond® ER)	✓	✓*
Morphine sulfate/naltrexone (Embeda®)	✓	✓
Oxycodone (OxyContin®)	✓	✓
Oxycodone (Xtampza ER®)	✓	✓
Oxycodone/naloxone (Targiniq ER®)	✓	–
Oxycodone/naltrexone (Troxyca® ER)	✓	✓*
Oxymorphone (Opana® ER)	-	✓
Tapentadol (Nucynta ER®)	-	✓

*Manufacturer reports launch scheduled for first half of 2017

Therapeutic Indications/Efficacy

An *in vitro* laboratory manipulation study was performed to assess the physical properties of MorphaBond® ER (morphine extended-release) to determine resistance to manipulation. MorphaBond® ER (morphine extended-release) and MS Contin® (morphine extended-release) tablets were compared in this study. Seven different household instruments were used for a maximum of five minutes on each formulation. In addition to use of the household tools, pre-treatment of the products with a standard kitchen microwave, freezer and oven were used to determine if these altered the difficulty level of manipulation. The primary endpoints were the average time and difficulty to physically manipulate MorphaBond® ER (morphine extended-release) and MS Contin® (morphine extended-release). The difficulty to manipulate the products was assessed using 10-point rating scale where 1 was “very easy” to manipulate and 10 represented “impossible” to manipulate. Time to manipulate was measured in seconds, and 300 seconds was the maximum time allowed. Values for difficulty to manipulate

MorphaBond® ER (morphine extended-release) tablets with instruments 1 through 7 were 8.6, 1, 7.4, 6.4, 10, 10 and 10, respectively compared to 1 for all values for MS Contin® (morphine extended-release). Values for time to manipulate MorphaBond® ER (morphine extended-release) tablets with instruments 1 through 7 were 300, 8.6, 60, 49, 300, 300 and 300, respectively compared to 14.4, 5, 7.4, 42.8, 9, 4.8 and 5.6 for MS Contin® (morphine extended-release).[2]

An *in vitro* laboratory study was performed to assess the primary endpoint of syringeability and extractability of morphine from intact, crushed and cut MorphaBond® ER (morphine extended-release) tablets compared to crushed MS Contin® (morphine extended-release) tablets. Crushed, cut and intact tablets were placed in vials with 1 mL or 5 mL of water with and without agitation for up to 30 minutes. The resultant substances were then assessed for and rated on a scale of 1 to 10 with 1 representing "very easy to syringe" and 10 representing "impossible to syringe." Crushed and cut MorphaBond® ER (morphine extended-release) tablets resulted in a viscous substance that was not syringeable, all with a difficulty level of 10 regardless of volume of water, use of agitation, or needle size (up to 18-gauge attempted). Dissolution of intact MorphaBond® ER (morphine extended-release) tablets resulted in a syringeable solution; however, a maximum of 13% of the morphine was released from intact tablets in 5 mL of agitated water after 30 minutes. Crushed MS Contin® (morphine extended-release) passed through the smallest needle used (27-gauge) with a difficulty level of 1 for both the 1 mL and 5 mL samples, and up to 70% of morphine was extracted after 10 minutes.[2]

In vitro large volume extraction studies were performed to assess extractability of morphine from both intact and ground MorphaBond® ER (morphine extended-release) tablets. One study evaluated the percentage of morphine released from intact and ground tablets in 30 mL in a panel of readily available household solvents, aqueous solvents, ethanol-based solutions and laboratory/organic solvents after 30 minutes. The highest mean amount of morphine extracted after 30 minutes in aqueous solutions was ≤ 18% from ground MorphaBond® ER (morphine extended-release) tablets. The highest mean amount of morphine extracted was seen in a solvent labeled "Household Solvent B". Numerical values were not reported for the amount of morphine extracted in Household Solvent B; however, a graph shows between 30% and 40% of morphine in both intact and ground MorphaBond® ER (morphine extended-release) tablets was released after 30 minutes. A separate *in vitro* large volume extraction study found that it took approximately six hours to release 75% of the active ingredient in MorphaBond® ER (morphine extended-release) which represented a much longer time than it took to release 75% of active ingredient from Hysingla ER® (hydrocodone extended-release), OxyContin® (oxycodone extended-release) and Embeda® (morphine extended-release/naltrexone) (30 minutes, 15 minutes and 5 minutes, respectively). In addition, manipulation of MorphaBond® ER (morphine extended-release) tablets reduced the mean amount of morphine released in common edible solvents compared to intact MorphaBond® ER (morphine extended-release) tablets by 2%. Of note, a major limitation of this study was that only one commonly injectable/ingestible solvent was used for comparison of the time to release 75% of active ingredient, which may introduce the possibility of bias in the selection of that solvent.[2]

A randomized, double-blind, double-dummy, placebo-controlled, four-way crossover study was conducted to assess the clinical abuse potential of crushed MorphaBond® ER (morphine extended-release) administered intranasally compared to intranasal placebo, crushed intranasal MS Contin® (morphine extended-release) and intact MorphaBond® ER (morphine extended-release) given by mouth. After a naloxone challenge and drug discrimination phase, 27 nondependent opioid users were randomized to one of four treatment sequences with at least seven day washout periods between each treatment. The primary endpoint was the mean maximum drug liking score (E_{max}) on the Visual Analogue Scale (VAS). Secondary endpoints included overall drug liking scores on the VAS, willingness to take drug again scores on the VAS, Drug Effects Questionnaire (DEQ) scores on the VAS, Addiction Research Center Inventory/Morphine Benzedrine Group (ARCI/MBG) subscale scores, and adverse events. Crushed MorphaBond® ER (morphine extended-release) used intranasally was associated with a statistically significant reduction in E_{max} VAS drug liking scores compared to crushed MS Contin® (morphine extended-release) (71.13 versus 84.79, respectively; $P<0.0001$). There was no statistically significant difference in E_{max} VAS drug liking scores between crushed MorphaBond® ER (morphine extended-

release) used intranasally and intact MorphaBond® ER (morphine extended-release) taken by mouth (71.13 versus 67.03, respectively; P=not significant). VAS scores on DEQ questions related to any effects, good effects and drug high were significantly lower with crushed MorphaBond® ER (morphine extended-release) used intranasally compared to crushed MS Contin® (morphine extended-release) (P=0.003, P=0.004, P=0.001, respectively.) VAS scores for overall drug liking and willingness to take drug again were statistically significantly lower for crushed MorphaBond® ER (morphine extended-release) used intranasally compared to crushed MS Contin® (morphine extended-release) (P=0.007 and 0.0341, respectively). There was no statistically significant difference in ARCI/MBG subscale scores between crushed MorphaBond® ER (morphine extended-release) used intranasally and crushed MS Contin® (morphine extended-release) (8.48 versus 10.56, respectively; P=0.0511). Adverse events were generally considered mild and common to opioids and opioids administered intranasally across all treatments.[4]

Pharmacokinetics/Pharmacogenomics

Absorption
The oral bioavailability of morphine is approximately 20 to 40%. When MorphaBond® ER (morphine extended-release) is given at a fixed dose and frequency steady-state is achieved in approximately one day.[1]

Distribution
The volume of distribution (VD) for oral morphine is approximately 3 to 4 L/kg. Plasma protein binding of morphine is approximately 30 to 35%. After absorption, morphine is distributed to the skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. In addition, morphine has been found to cross the placenta and be excreted into the breast milk.[1]

Metabolism
Morphine undergoes glucuronidation to morphine-3-glucuronide (M3G, approximately 50%) and morphine-6-glucuronide (M6G, approximately 5 to 15%). Minor pathways of metabolism include sulfation to morphine-3-etheral sulfate and demethylation. M6G is an active metabolite, but has poor ability to cross the blood-brain barrier.[1]

Excretion
Morphine is primarily excreted as M3G in the urine; however, approximately 10% of a dose of morphine is excreted unchanged in the urine. A minor pathway of excretion occurs as glucuronide conjugate in the bile. In addition, there is a minor amount of enterohepatic recycling.[1]

Food Effects
The effect of food upon the bioavailability of MorphaBond® ER (morphine extended-release) has not been evaluated for all strengths; however, administration of a single dose of MorphaBond® ER (morphine extended-release) with a high fat meal resulted in a 33% increase in peak plasma concentration (C_{max}) of morphine with no change in overall exposure (AUC) compared to administration in a fasted state.[1]

Effects of Tampering
The median time to peak plasma concentration (T_{max}) for morphine was identical between crushed MorphaBond® ER (morphine extended-release) intranasally and intact MorphaBond® ER (morphine extended-release) by mouth at 1.6 hours (ranges 1.0 to 3.1 and 0.5 to 3.1, respectively). The overall plasma exposure to morphine and M6G (AUC_{0-t} morphine + AUC_{0-t} M6G) was approximately 37% lower with crushed MorphaBond® ER (morphine extended-release) intranasally compared to intact MorphaBond® ER (morphine extended-release) by mouth (620.3 ng●hr/mL versus 938.8 ng●hr/mL, respectively). In addition, the mean (SD) C_{max} for morphine was numerically higher with crushed MorphaBond® ER (morphine extended-release) intranasally (26.2 ng/mL [11.2]) compared to intact MorphaBond® ER (morphine extended-release) by mouth (18.6 ng/mL [5.7]); however, this was not statistically significant.[2,9]

Pharmacogenomic Considerations:
Evidence is available that suggests certain genetic variants may be related to requirement of higher doses of morphine for adequate analgesia; however, this evidence is based on studies with small sample sizes. A large study of 2,294 cancer patients, 830 of which were on morphine, was conducted to evaluate whether genetic variants were associated with opioid doses. The study failed to replicate previous findings of genetic associations related to opioid efficacy (including morphine), suggesting that pharmacogenetics of opioids need not be considered in clinical decision making.[10,11]

Table 2. Pharmacokinetics[1,9,12]

Generic Name	T_{max} (hours)*	Duration (hours)	Clearance (mL/min/kg)	Active Metabolites	Serum Half-Life (hours)†
Morphine	1.6	12	20 to 30	Morphine-6-glucuronide (M6G)	9.5

*Median T_{max} for single dose of 60 mg
†Mean serum half-life for single dose of 100 mg tablet

Special Populations

Table 3. Special Populations[1]

Population	Precaution
Pregnancy/Lactation	The prolonged use of opioids during pregnancy may result in physical dependence in the neonate and neonatal opioid withdrawal syndrome after birth. Opioids cross the placenta and may result in respiratory depression and psycho-physiologic effects in neonates. Based upon animal data, advise pregnant women of the potential risk to a fetus. Data from a population-based prospective cohort study that included 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy did not indicate increased risk for congenital malformations. This study does not establish the absence of risk because of methodological limitations, including the small sample size and non-randomized design. There are no data available for MorphaBond® ER (morphine extended-release) in pregnant women regarding potential for birth defects or miscarriage. Morphine is present in breast milk; lactation studies have not been conducted with extended-release formulations of morphine, including MorphaBond® ER (morphine extended-release). Because of the potential serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with MorphaBond® ER (morphine extended-release).
Females and Males of Reproductive Potential	Chronic use of opioids may cause reduced fertility in males and females of reproductive potential. It is not known whether effects on fertility are reversible. Animal data indicates morphine adversely affected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats.

Population	Precaution
Children	Safety and efficacy of MorphaBond® ER (morphine extended-release) have not been established in patients below the age of 18 years.
Elderly	Clinical studies of morphine extended-release did not include a sufficient amount of subjects aged 65 and older to determine whether they respond differently from younger subjects. Morphine is substantially excreted by the kidney, and risk of adverse reactions to morphine may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function. As such, care should be taken in dose selection, and it may be useful to monitor renal function.
Hepatic Impairment	The pharmacokinetics of morphine is known to be significantly altered in patients with cirrhosis. Start these patients at a lower than usual dosage of MorphaBond® ER (morphine extended-release) and titrate slowly, monitoring for signs of respiratory depression, sedation and hypotension.
Renal Impairment	The pharmacokinetics of morphine is altered in patients with renal impairment. Start these patients at a lower than usual dosage of MorphaBond® ER (morphine extended-release) and titrate slowly, monitoring for signs of respiratory depression, sedation and hypotension.

Dosage Forms

Table 4. Availability, Storage and Handling[1]

Dosage Form	Strength	Special Handling or Storage
Extended-release tablet	15 mg 30 mg 60 mg 100 mg	Store at 25°C (77°F); excursions between 15° and 30°C (59° and 86°F) are permitted. Dispense and store in tight, light-resistant container with child-resistant closure.

Dosage Range

Table 5. Dosing and Administration[1]

Adult Dose	Pediatric Dose	Renal Dose	Hepatic Dose
Management of pain that is severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate: Initial: 15 mg every 12 hours Maintenance: individually titrate to a dose that provides adequate	Safety and efficacy in pediatric patients have not been established.	Start with lower than usual dosage and titrate slowly while monitoring for respiratory depression, sedation and hypotension.	Start with lower than usual dosage and titrate slowly while monitoring for respiratory depression, sedation and hypotension.

Adult Dose	Pediatric Dose	Renal Dose	Hepatic Dose
analgesia and minimizes adverse reactions every 1 to 2 days			

Dosing Considerations:

Conversion from other oral morphine formulations to MorphaBond® ER (morphine extended-release)

Patients receiving other oral morphine formulations may be converted to MorphaBond® ER (morphine extended-release) by administering one-half of the patient's total daily oral morphine dose as MorphaBond® ER (morphine extended-release) every 12 hours.[1]

Conversion from other opioids to MorphaBond® ER (morphine extended-release)

Discontinue all other around-the-clock opioid drugs when MorphaBond® ER (morphine extended-release) therapy is initiated.[1]

There are no established conversion ratios for conversion from other opioids to MorphaBond® ER (morphine extended-release) defined by clinical trials. Initiate dosing using MorphaBond® ER (morphine extended-release) 15 mg every 12 hours.[1]

It is safer to underestimate a patient's 24-hour oral morphine dosage and provide rescue medication than to overestimate the 24-hour oral morphine dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is inter-patient variability in the relative potency of opioid drugs and formulations.[1]

Conversion from parenteral morphine or other opioids (parenteral or oral) to MorphaBond® ER (morphine extended-release)

When converting from parenteral morphine to MorphaBond® ER (morphine extended-release) consider that between 2 to 6 mg of oral morphine may be required to provide analgesia equivalent to 1 mg of parenteral morphine. Typically, a dose of morphine that is approximately three times the previous daily parenteral morphine requirement is sufficient.[1]

When converting from other parenteral or oral non-morphine opioids to MorphaBond® ER (morphine extended-release) specific recommendations for ratios are not available because of a lack of systematic evidence for these types of analgesic substitutions. Published relative potency data are available, but such ratios are approximations. In general, begin with half of the estimated daily morphine requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release morphine.[1]

Conversion from methadone to MorphaBond® ER (morphine extended-release)

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.[1]

Discontinuation of MorphaBond® ER (morphine extended-release)

When a patient no longer requires therapy with MorphaBond® ER (morphine extended-release), taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue MorphaBond® ER (morphine extended-release).[1]

Precautions

Boxed Warning for MorphaBond® ER (morphine extended-release)[1]

WARNING
Addiction, Abuse and Misuse MorphaBond® ER (morphine extended-release) exposes users to risks of addiction, abuse, and misuse,

WARNING
which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for these behaviors and conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow MorphaBond® ER (morphine extended-release) tablets whole; crushing, chewing, or dissolving MorphaBond® ER (morphine extended-release) can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Ingestion Accidental ingestion of MorphaBond® ER (morphine extended-release), especially by children, can result in fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of MorphaBond® ER (morphine extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of MorphaBond® ER (morphine extended-release) and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 6. Warnings/Precautions[1]

Warning/ Precaution	Addiction, abuse and misuse; as an opioid, MorphaBond® ER (morphine extended-release) exposes users to the risks of addiction, abuse and misuse. As extended-release products such as MorphaBond® ER (morphine extended-release) deliver the opioid over an extended period of time, there is a greater risk of overdose and death due to the larger amount of morphine present. Although the risk of addiction in any individual is not known, it can occur in patients appropriately prescribed MorphaBond® ER (morphine extended-release) at the recommended dosages. Patients at increased risk may be prescribed opioids, but use in such patients necessitates intensive counseling regarding the risks and appropriate use of MorphaBond® ER (morphine extended-release), along with intensive monitoring for signs of addiction, abuse, and misuse. Abuse or misuse of MorphaBond® ER (morphine extended-release) by crushing, chewing, snorting, or injecting the dissolved product in may result in overdose and death.
	Life-threatening respiratory depression; serious, life-threatening or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal

	respiratory depression can occur at any time during the use of MorphaBond® ER (morphine extended-release), the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of MorphaBond® ER (morphine extended-release). To reduce the risk of respiratory depression, proper dosing and titration of MorphaBond® ER (morphine extended-release) are essential. Overestimating the MorphaBond® ER (morphine extended-release) dosage when converting patients from another opioid product can result in a fatal overdose with the first dose. Accidental ingestion of even one dose of MorphaBond® ER (morphine extended-release), especially by children, can result in respiratory depression and death due to an overdose of morphine.
	Neonatal opioid withdrawal syndrome; prolonged use of MorphaBond® ER (morphine extended-release) during pregnancy can result in withdrawal in the neonate. Unlike opioid withdrawal syndrome in adults, neonatal opioid withdrawal syndrome may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure appropriate treatment will be available.
	Risks due to concomitant use with benzodiazepines or other CNS depressants; profound sedation, respiratory depression, coma and death may result if MorphaBond® ER (morphine extended-release) is used concomitantly with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, tranquilizers, muscle relaxants, general anesthetics, anxiolytics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when MorphaBond® ER (morphine extended-release) is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid

	abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.
	Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic or debilitated patients; patients with chronic pulmonary disease - MorphaBond® ER (morphine extended-release)-treated patients with significant chronic pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression are at an increased risk of decreased respiratory drive including apnea, even at recommended dosages of MorphaBond® ER (morphine extended-release). Elderly, cachectic or debilitated patients - life-threatening respiratory depression is more likely to occur in elderly, cachectic or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely; particularly when initiating and titrating MorphaBond® ER (morphine extended-release) and when MorphaBond® ER (morphine extended-release) is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.
	Interaction with monoamine oxidase inhibitors (MAOIs); MAOIs may potentiate the effects of morphine, including respiratory depression, coma and confusion. MorphaBond® ER (morphine extended-release) should not be used in patients taking MAOIs or within 14 days of stopping such treatment.
	Adrenal insufficiency; cases of adrenal insufficiency have been reported with opioid use, often after at least one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms, such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible and treat with physiologic replacement of corticosteroids. The patient should be weaned off of the opioid and corticosteroid treatment should be continued until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify an opioid as being more likely to be associated with adrenal insufficiency.
	Severe hypotension; MorphaBond® ER (morphine extended-release) may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure is already compromised by a reduced blood volume or concomitant CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of MorphaBond® ER (morphine extended-release). Avoid use in patients with circulatory shock, as MorphaBond® ER (morphine extended-release) may cause vasodilation that further reduces cardiac output and blood pressure in these patients.
	Risks of use in patients with increased intracranial pressure, brain tumors, head injury or impaired consciousness; in patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), MorphaBond® ER (morphine extended-release) may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor these patients for signs of sedation and respiratory depression, particularly when initiating therapy with MorphaBond® ER (morphine extended-release). Opioids may obscure the clinical course in a patient with a head injury. Avoid the

	use of MorphaBond® ER (morphine extended-release) inpatients with impaired consciousness or coma.
	Increased risk of seizures in patients with seizure disorders; the morphine in MorphaBond® ER (morphine extended-release) may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during treatment with MorphaBond® ER (morphine extended-release).
	Withdrawal; avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing MorphaBond® ER (morphine extended-release), gradually taper the dosage; do not abruptly discontinue this agent.
	Risks of driving and operating machinery; MorphaBond® ER (morphine extended-release) may impair the mental or physical abilities necessary to perform potentially hazardous activities, such as driving a car or operating machinery. Patients should be warned not to drive or operate dangerous machinery unless they are tolerant to the effects of this agent and know how they will be affected by it.

Contraindications

Table 7. Contraindications[1]

Contraindication	
	MorphaBond® ER (morphine extended-release) is contraindicated in patients with significant respiratory depression.
	MorphaBond® ER (morphine extended-release) is contraindicated in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
	MorphaBond® ER (morphine extended-release) is contraindicated in patients using MAOIs or that have used MAOIs within the last 14 days.
	MorphaBond® ER (morphine extended-release) is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
	MorphaBond® ER (morphine extended-release) is contraindicated in patients with hypersensitivity to morphine.

Adverse Effects

The safety and efficacy of MorphaBond® ER (morphine extended-release) was based upon data for MS Contin® (morphine extended-release). As such, there are no adverse reactions that have been reported that are specific to MorphaBond® ER (morphine extended-release), and the adverse effect profile is expected to be similar to that of MS Contin® (morphine extended-release) and other morphine products.

In clinical trials, the most common adverse reactions associated with morphine extended-release were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoric mood.[1]

Drug Interactions

Table 8. Drug Interactions[1,12]

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Anticholinergic Drugs	Major	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when using opioids concomitantly with anticholinergic agents.
Benzodiazepines/ Other CNS Depressants	Major	Due to their additive pharmacologic effect, the concomitant use of opioids and benzodiazepines or other CNS depressants may increase the risk of respiratory depression, profound sedation, coma and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, and limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation.
Cimetidine	Major	Concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma and death. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dose of MorphaBond® ER (morphine extended-release) and/or cimetidine as necessary.
Cyclosporine	Major	Concurrent use of cyclosporine and morphine may result in increased morphine exposure, increased risk of abnormalities or malfunction of the nervous system.
Mixed Agonist/Antagonist and Partial Agonist Opioids	Major	The use of these agents may reduce the analgesic effect of MorphaBond® ER (morphine extended-release) or precipitate withdrawal symptoms. Avoid concomitant use with these agents.
Monoamine Oxidase Inhibitors (MAOIs)	Major	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). Do not use MorphaBond® ER (morphine extended-release) in patients taking MAOIs or within 14 days of stopping MAOIs.
Muscle Relaxants	Major	Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and result in an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected. Decrease the dose of MorphaBond® ER (morphine extended-release) and/or the muscle relaxant as necessary.
P-glycoprotein (P-gp) inhibitors (e.g., quinidine)	Major	Concomitant use of P-gp inhibitors can increase the exposure to morphine by approximately two-fold and can increase the risk of hypotension, respiratory depression, profound sedation, coma and death. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MorphaBond® ER (morphine extended-release) and/or the P-gp inhibitor as necessary.
Serotonergic Drugs	Major	Concomitant use of opioids and serotonergic drugs has resulted in serotonin syndrome. If concomitant use is necessary, carefully observe the patient, particularly during treatment initiation and dose adjustments. If serotonin syndrome is suspected, discontinue MorphaBond® ER (morphine extended-release).

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Diuretics	Moderate	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure. Increase the dose of the diuretic as necessary.
Esmolol	Moderate	Concurrent use of esmolol and morphine may result in esmolol toxicity (bradycardia, hypotension).
Gabapentin	Moderate	Concurrent use of gabapentin and morphine may result in increased gabapentin concentrations.
Ginseng	Moderate	Concomitant use of opioids with ginseng may result in decreased efficacy of analgesia of opioids.
Kava	Moderate	Concomitant use of opioids with kava may result in increased CNS depression.
Rifampin	Moderate	Concomitant use of morphine and rifampin may result in loss of morphine efficacy.
Somatostatin	Moderate	Concurrent use of somatostatin and morphine may result in reduced analgesia with morphine.
Trospium	Moderate	Concurrent use of morphine and trospium may result in increased serum concentrations of morphine and/or trospium, potentially increasing risk of paralytic ileus.
Valerian	Moderate	Concomitant use of opioids with valerian may result in increased CNS depression.
Yohimbine	Moderate	Concurrent use of morphine and yohimbine may result in increased analgesic and adverse effects of morphine.

*Severity rating per Micromedex

Patient Monitoring Guidelines

Before starting therapy with an opioid, individuals should be evaluated for potential signs of addiction, abuse or misuse of medications; risks are increased in patients with a personal or family history of substance abuse or mental illness, but the potential for these risks should not prevent the proper management of pain. If therapy with an opioid is started, they should continue to be monitored frequently for any changes in behavior. While the individual is receiving opioid analgesics they should be monitored for adequacy of analgesia as well as continually assessed for the need of continued opioid treatment.[1]

The following signs and symptoms should be monitored during therapy with opioids:

- respiratory depression and sedation; especially within the first 24 to 72 hours after initiating therapy and following dose increases; and particularly in high risk patients (elderly, cachectic, or debilitated patients, those with preexisting respiratory depression or otherwise significantly reduced respiratory reserve, and those who may be susceptible to the intracranial effects of CO_2 retention)
- exacerbation of biliary tract disease
- hypotension; in ambulatory patients and in those whose ability to maintain blood pressure has been compromised; especially after initiating therapy or titrating the dose
- worsened seizure control; in patients with a history of seizure disorders
- signs of abuse, misuse and addiction

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